Anesth Prog 41:6–10 1994

SCIENTIFIC REPORT

Effective Postoperative Pain Prevention through Administration of Bupivacaine and Diclofenac

Tapio Hyrkäs, MD, DDS,* Pekka Ylipaavalniemi, DDS, PhD,*
Valle J. Oikarinen, MD, DDS, PhD, FDSRCS (Eng.),* and Ilari Paakkari, MD, PhD†
*Department of Oral and Maxillofacial Surgery and †Department of Pharmacology and Toxicology, University of Helsinki, Helsinki, Finland

The efficacies of bupivacaine and lidocaine together with a preoperatively administered single-dose oral combination of normal- and sustained-release preparations of diclofenac in preventing postoperative pain after third molar removal were compared in a double-blind crossover study. Bilaterally impacted lower third molars were removed in two sessions. Each patient was given one type of local anesthetic on one session and the other in the second. Pain was recorded using a visual analog scale. When the diclofenac combination (150 mg) was given before the operation, postoperative analgesia was better with bupivacaine plus diclofenac than with lidocaine plus diclofenac. Twenty-five out of 40 patients preferred bupivacaine to lidocaine for local anesthesia. It is possible to achieve effective postoperative pain prevention by combining bupivacaine and preoperative normal- and sustained-release preparations of diclofenac.

Control of postoperative pain in outpatients undergoing oral and maxillofacial surgery is usually achieved by administration of a short-acting local anesthetic and oral analgesics as needed. After the surgical removal of impacted mandibular third molar teeth, pain intensity is maximal 3 to 5 hr after the end of surgery,[1] shortly after the effect of the short-acting local anesthetic has worn off. Theoretically, it should be possible to enhance postoperative pain control by lengthening the period of analgesia. This is achieved by using a long-acting anesthetic such as bupivacaine or etidocaine. Studies of long-acting local anesthetics have given encouraging results; investigators have demonstrated significant pain reduction with bupivacaine[2–6] and etidocaine.[5,7] In most studies there was no antiinflammatory premedication,[2,3,5–7] but one reported effective pain reduction by combining a low dose of diflunisal with bupivacaine,[4] and another used flurbiprofen with etidocaine.[8] Preoperative administration of nonsteroidal antiinflammatory drugs (NSAIDs) is not a routine in many studies, perhaps due to fear of complications like alveolitis and postoperative bleeding. We have shown that when lidocaine is used for local anesthesia, oral pretreatment with the NSAID diclofenac combination of fast-acting and sustained-release formulations resulted in a very low level of postoperative pain.[9] To achieve even lower pain levels in this kind of ambulatory surgery seems to be difficult. We have not seen reports dealing with the use of this type of NSAID combination together with bupivacaine, although this combination would theoretically yield even greater pain suppression.

In this report we present a double-blind crossover study in which the effect on postoperative pain of this diclofenac combination plus bupivacaine was compared with the diclofenac combination plus lidocaine.

METHODS

We studied 44 patients, each undergoing the surgical removal of two impacted lower third molars (classes A II, B I, and B II of Pell and Gregory's classification of impacted third molars[10]), which involved osteotomy. (The difficulty of tooth removal increases from class I to II and from A to B, respectively.) Panoramic radiographs were taken. Groups studied were homogeneous in regard to age, degree of tooth retention, and duration of operation. Patient characteristics are shown in Table 1. Exclusion criteria included allergy to diclofenac, peptic ulcer, asthma, pregnancy, and chronic use of analgesic or antiinflammatory medication. In the patient population thus included there were no reports of occasional use of sedatives, analgesics, or antiinflammatory agents.

Received March 10, 1993; accepted for publication July 13, 1993.
Address correspondence to Dr. Tapio Hyrkäs, Department of Oral and Maxillofacial Surgery, University of Helsinki, P.O. Box 41, FIN-00014, Finland.

ISSN 0003-3006/94/$7.00

Table 1. Patient Characteristics

	Group A	*Group B*
Women	14	12
Men	10	8
n	24	20
Age (yr)[a]	24.3 ± 0.5	23.9 ± 0.8
Weight (kg)[a]	65.0 ± 2.5	64.5 ± 1.7
Height (cm)[a]	171.8 ± 1.8	172.8 ± 1.5

Group A subjects received bupivacaine for the first operation and lidocaine for the second; group B received the reverse order.

[a] Mean ± standard error.

The trial protocol was approved by the local ethical committee and was conducted in accordance with the Declarations of Helsinki and Tokyo. Informed written consent was obtained from each patient. The study was conducted on a double-blind, randomized crossover basis. A single impacted tooth was removed in each of two sessions. The period of time between each operation averaged 2 mo. Each patient was given one type of local anesthetic in one session and the other in the second. The solutions were prepared immediately before the operation by a nurse not involved in the actual study. The solutions were identical in appearance and were coded and assigned to the patients according to a prerandomization list. Accordingly, neither the surgeon, his assistant, nor the patient were aware of the drug being used. We determined the effects of trial medications on postoperative pain. The second operation was done in order to determine patient preferences for the trial medications.

Each patient was given a 50-mg diclofenac normal enterotablet and a sustained-release 100-mg tablet (Voltaren, Ciba-Geigy, Basle, Switzerland) 20 min before surgery. Patients were placed in groups, each involving a different mode of mandibular conduction anesthesia. Group A patients received bupivacaine (5 mg/mL) containing 5 μg/mL epinephrine (Marcaine, Astra, Södertälje, Sweden); Group B patients received lidocaine (20 mg/mL) containing 12.5 μg/mL epinephrine (Xylocain, Astra). For local buccal infiltration anesthesia, lidocaine with epinephrine was used in all patients. The volumes injected were 3 mL for nerve block anesthesia and 1.8 mL for infiltration anesthesia. All operations were carried out by the same surgeon. No sedative premedication was used. All patients received oral antibiotics postoperatively (660 mg phenoxymethyl penicillin or 400 mg erythromycin acistrate), to be taken three times daily, for 1 wk. An analgesic containing 300 mg aminopyrine, 30 mg codeine phosphate, 50 mg phenobarbital, and 100 mg caffeine (Dolorin, Orion Pharmaceuticals, Espoo, Finland) was given if needed to relieve pain not controlled by the tested medications. The number of patients taking these tablets was used as one measure of the efficacy of the medications tested.

Patients recorded pain using a visual analog scale (VAS; 0 mm = no pain, 100 mm = intolerable pain) hourly for 8 hr after the operation. During the first and second days after surgery, pain was recorded morning and evening. Inability to eat and problems in mouth opening were recorded during the first and second postoperative days. Both early and late side effects were recorded. Patients were also asked about their treatment preference.

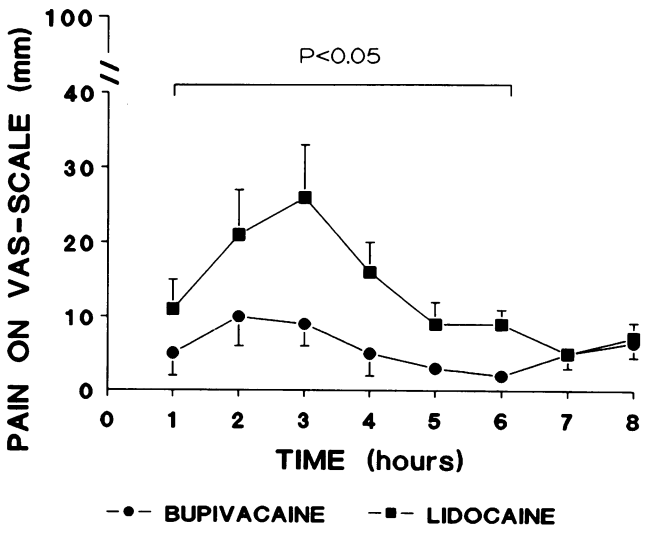
Data were subjected to two-way analysis of variance (ANOVA) for repeated measures. Means of groups were compared using Student's *t*-test. For analysis of the frequencies between groups, the χ^2 test was used.

RESULTS

In relation to the first operation, administration of bupivacaine plus diclofenac resulted in significantly greater pain relief than did lidocaine plus diclofenac during the first 6 hr (Figure 1). Thereafter, pain relief was similar to that afforded by lidocaine plus diclofenac. The difference was greatest 3 hr after operation.

In relation to the second operation, bupivacaine plus diclofenac was significantly better for pain relief only during the first and second hours after operation (Figure 2). There was a significant increase in pain toward nightfall on the first day after the operation in both groups (Figure 3). In general, VAS pain scores were lower after the second operation. The difference was greatest with the

Figure 1. Effect of local anesthesia with bupivacaine (n = 24) or lidocaine (n = 20) and of diclofenac administration on pain perception as shown by visual analog scale (VAS) scores after the first operation. Analysis of variance for repeated measures (1 to 6 hr): group, $P < 0.05$; time, $P < 0.001$; interaction, $P = 0.39$.



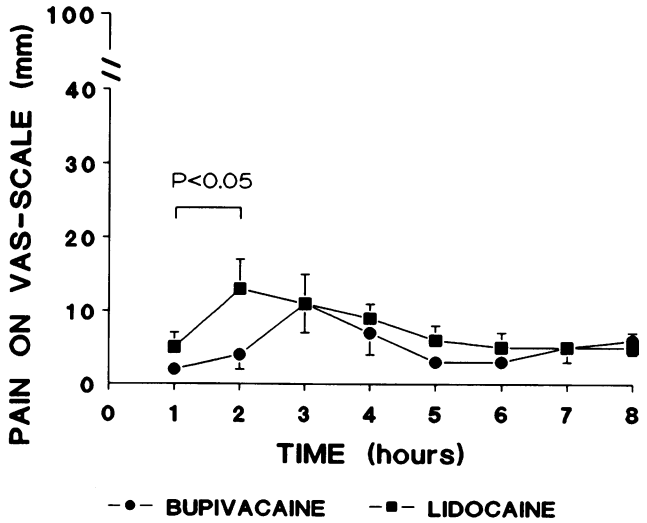
lidocaine plus diclofenac treatment: 25.8 ± 6.6 mm (mean ± S.E., 3 hr after first operation) vs 11.5 ± 3.5 mm (second operation, $P = 0.058$).

After the first operation, 8/24 and 7/20 patients needed rescue medication in the bupivacaine plus diclofenac and lidocaine plus diclofenac groups, respectively. After the second operation the corresponding numbers were 7/19 and 7/21. Four patients did not want to participate in the second part of the study. There was no statistically significant difference in the use of rescue medication at any given time point. Five patients needed rescue medication after both the first and second operation.

The patients' ability to eat was slightly to moderately limited during the first and second days after surgery. There were no statistically significant differences between treatment groups. With respect to mouth opening (55.1 ± 1.3 mm for bupivacaine plus diclofenac and 49.5 ± 1.1 mm for lidocaine plus diclofenac), baselines for the groups differed significantly ($P < 0.001$). After surgery, mouth opening was decreased maximally to 37.9 ± 2.1 mm (bupivacaine plus diclofenac) and 31.2 ± 2.3 mm (lidocaine plus diclofenac). The changes were highly significant in relation to baseline levels ($P < 0.001$). However, the magnitude of the change was not significantly different between the two groups ($P = 0.82$).

Three patients receiving bupivacaine plus diclofenac and five receiving lidocaine plus diclofenac reported nausea. Five of these patients had needed to take the rescue analgesic. No other side effects were reported. Twenty-five patients preferred bupivacaine and nine lidocaine ($P < 0.001$).

Figure 2. Effect of local anesthesia with bupivacaine (n = 19) or lidocaine (n = 21) and of diclofenac administration on pain perception as shown by visual analog scale (VAS) scores after the second operation. Analysis of variance for repeated measures (1 to 2 hr): group, $P < 0.05$; time, $P < 0.01$; interaction, $P = 0.058$.



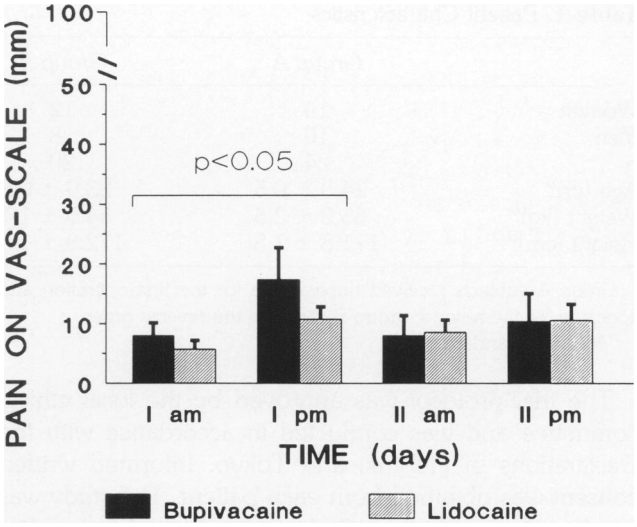


Figure 3. Effect of local anesthesia with bupivacaine (n = 24) or lidocaine (n = 20) on pain perception as shown by visual analog scale (VAS) scores on the first and second days after the first operation. Analysis of variance for repeated measures (first day am and pm): group, $P = 0.20$; time, $P < 0.05$; interaction, $P = 0.44$.

DISCUSSION

The findings of the present study show that use of the long-acting local anesthetic bupivacaine resulted in additional suppression of postoperative pain when added to pretreatment with a combination of normal- and sustained-release diclofenac preparations. The efficacy of such a combination of diclofenac was shown in a previous study where rapidly acting diclofenac (potassium salt) plus the sustained-release preparation resulted in substantial protection against pain for up to 8 hr after surgery when lidocaine was used for conduction anesthesia.[9] In that study the diclofenac combination administered orally was equally effective as the same dose in combination of oral and intramuscular administration. This type of orally administrated NSAID pretreatment is currently part of our usual operative regimen. Results of the present study are in agreement with those of Cooper et al.[11] They reported effective pain prevention through administration of a single dose of controlled-release ibuprofen after dental impaction surgery. Our results also confirm those of Dionne et al., who suggested that the NSAID flurbiprofen and the local anesthetic etidocaine act in a complementary manner to suppress postoperative pain.[8]

The analgesic effect of bupivacaine in lower third molar surgery has been reported to last about 7[12] to 8 hr.[5] Other studies report a longer duration of anesthesia in mandibular blocks vs maxillary infiltrations with bupivacaine,[13] but this agent does not fulfill the concept of a

long-acting agent when used for oral infiltration anesthesia.[14] Caruso et al[15] reported that the duration of anesthesia with bupivacaine varies widely. This duration of action would nevertheless cover the time of maximum pain (3 to 5 hr postoperatively)[1] and should keep pain VAS scores to a minimum (about 15). Maximum pain relief would therefore be expected following use of bupivacaine and preoperative administration of normal enterotablet and sustained-release formulations of diclofenac that result in maximum plasma drug concentrations 1.5 to 2.5 hr[16] and 6 to 8 hr, respectively, after administration (data on file, Ciba-Geigy). In the present study, all patients were given diclofenac preoperatively because we think that it is unethical to leave patients without effective pain medication in this kind of surgery, where postoperative pain is often severe. Therefore, the only variable of this study was the local anesthetic solution used, and there were no controls to determine the exact contribution of the diclofenac to the overall pain relief. This makes it easier to evaluate the results. The problem in interpretating many previous studies reported is that variables such as the use of sedative medication[7] or general anesthesia[12] and the number of third molar teeth removed at the same session[7,15] are not equal.

The results of this study support the idea that pain after surgery is best minimized by use of a long-acting local anesthetic and preoperative administration of a NSAID. VAS scores during the first 8 hr after the operation were below 10 mm, surprisingly low in this kind of surgery. One explanation for this might be that neural blockade with bupivacaine extends far beyond the time of maximum pain intensity, with diclofenac derivatives having been absorbed and peak plasma concentrations reached before the local anesthetic effect wanes. This would be in accordance with the kinetic properties of the diclofenac formulations.

Bupivacaine was used for mandibular conduction anesthesia, and lidocaine for buccal infiltration. In our pilot trial, bupivacaine (5 mg/mL) plus epinephrine (5 μg/mL) was not suitable for buccal infiltration anesthesia at the operative site because hemostasis was inadequate and bone analgesia was weak. Similar problems with bleeding during surgery have been reported with the use of bupivacaine with epinephrine in periodontal surgery,[17] and with etidocaine plus 5 μg/mL epinephrine used alone or in conjunction with flurbiprofen[8,18] for third molar surgery. Danielsson et al[5] reported adequate local ischemia in 90% of patients administered bupivacaine with epinephrine. We therefore used bupivacaine plus epinephrine for conduction anesthesia and lidocaine plus epinephrine for local infiltration to ensure good local hemostasis. The bleeding seen in our pilot trial, when bupivacaine was used for infiltration anesthesia, was probably a result of its marked vasodilating property and the low epinephrine concentration of the formulation available (5 μg/mL).

There were only slight differences in pain intensity during the first and second days after the operation. This is in accordance with the short duration of pain in this kind of surgery.[19] The lower pain intensities in the two groups after the second operation can be explained by a familiarity with the operation and postoperative sequelae.

Our patients' strong preference for bupivacaine showed that they did not perceive the prolonged period of anesthesia as a disadvantage. This finding is in agreement with the results of Danielsson et al,[5] who reported that 58% of their patients assessed the duration of anesthesia with bupivacaine as adequate and 36% considered it too long. It disagrees with the results of Rosenquist et al,[4] who reported no difference in patient preference.

We conclude that it is possible to achieve an almost pain-free postoperative period by combining normal- and sustained-release diclofenac derivatives and bupivacaine without increasing the incidence of side effects.

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